WHAT ARE LC-FAOD?

Long-Chain Fatty Acid Oxidation Disorders

LC-FAOD: A group of rare, life-threatening autosomal recessive disorders[1-4]

LC-FAOD result from **defective enzymes** involved in the transport and catabolism of long-chain fatty acids (LCFAs)—leading to **energy depletion** and a depletion of intermediate pools of the tricarboxylic acid (TCA) cycle.[1,3,4]

CARNITINE TRANSPORT DISORDERS[5,6]

CPT I deficiency[2,5]

Cause: Mutations in the *CPT1A* gene
Estimated incidence: 1:750,000 to 1:2,000,000

CACT deficiency[2,7]

Cause: Mutations in the *SLC25A20* gene
Estimated incidence: 1:750,000 to 1:2,000,000

CPT II deficiency[2,5]

Cause: Mutations in the *CPT2* gene
Estimated incidence: 1:750,000 to 1:2,000,000

BETA-OXIDATION DISORDERS[5]

VLCAD deficiency[2,5]

Cause: Mutations in the *ACADVL* gene
Estimated incidence: 1:85,000

TFP deficiency[2,5]

Cause: Mutations in both the *HADHA* and *HADHB* genes, leads to defects in the entire TFP complex
Estimated incidence: 1:750,000

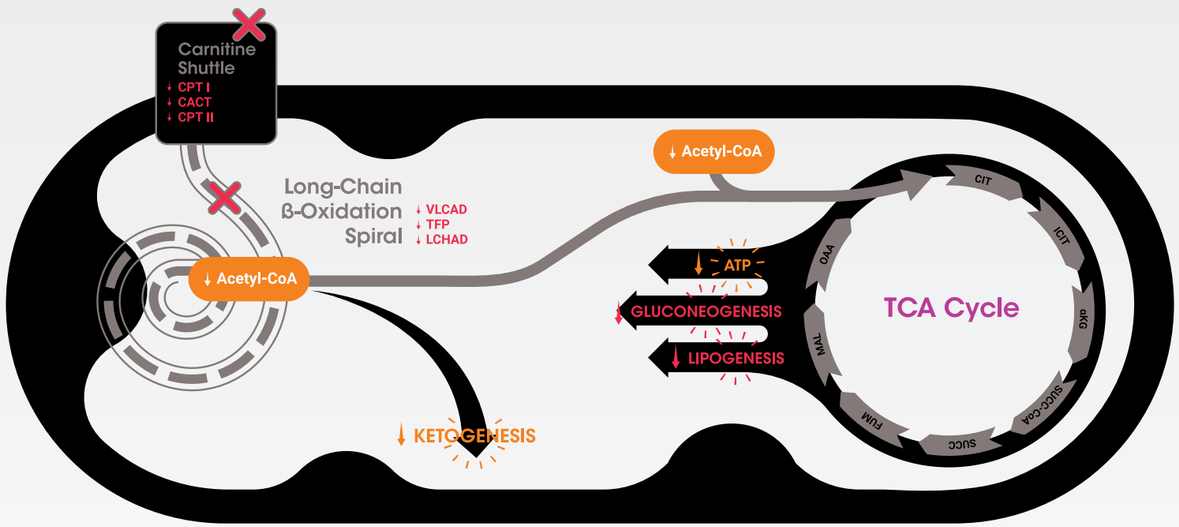
LCHAD deficiency[2,5]

Cause: Mutations in the *HADHA* gene, which encodes for a subunit of TFP
Estimated incidence: 1:250,000

CACT=carnitine-acylcarnitine translocase; CPT=carnitine palmitoyltransferase; LCHAD=long-chain 3-hydroxyacyl-CoA; TFP=trifunctional protein; VLCAD=very long-chain acyl-CoA dehydrogenase.

THE CAUSE

Unbalanced metabolism in LC-FAOD impairs energy production[3,4,8]



ENZYME DEFICIENCIES

LC-FAOD are caused by specific enzyme deficiencies in the carnitine shuttle system or the long-chain β-oxidation spiral.[1,9]

COMPROMISED LCFA METABOLISM

Impaired enzyme activity limiting normal metabolism of LCFAs into acetyl-CoAs results in[4,10]:

- Lower ATP production
- Impaired ketogenesis

TCA CYCLE IMBALANCE

Enzyme deficiencies can disrupt the anaplerosis/cataplerosis balance, leading to[4,11,12]:

- Accumulation of toxic metabolites
- Lack of replenishing substrates in the TCA intermediate pools

IMPAIRED ENERGY PRODUCTION

Incomplete TCA cycle processing may impair[3,4,8,13,14]:

- Gluconeogenesis
- Lipogenesis

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Acetyl-CoA=acetyl coenzyme A; αKG=alpha-ketoglutarate; ATP=adenosine triphosphate; CACT=carnitine-acylcarnitine translocase; CITR=citrate; CPT=carnitine palmitoyltransferase; FUM=fumarate; ICIT=isocitrate; LCHAD=long-chain 3-hydroxyacyl-CoA dehydrogenase; MAL=malate; OAA=oxaloacetate; SUCC=succinate; SCoA=succinyl-CoA; TCA=tricarboxylic acid; TFP=mitochondrial trifunctional protein; VLCAD=very long-chain acyl-CoA dehydrogenase.

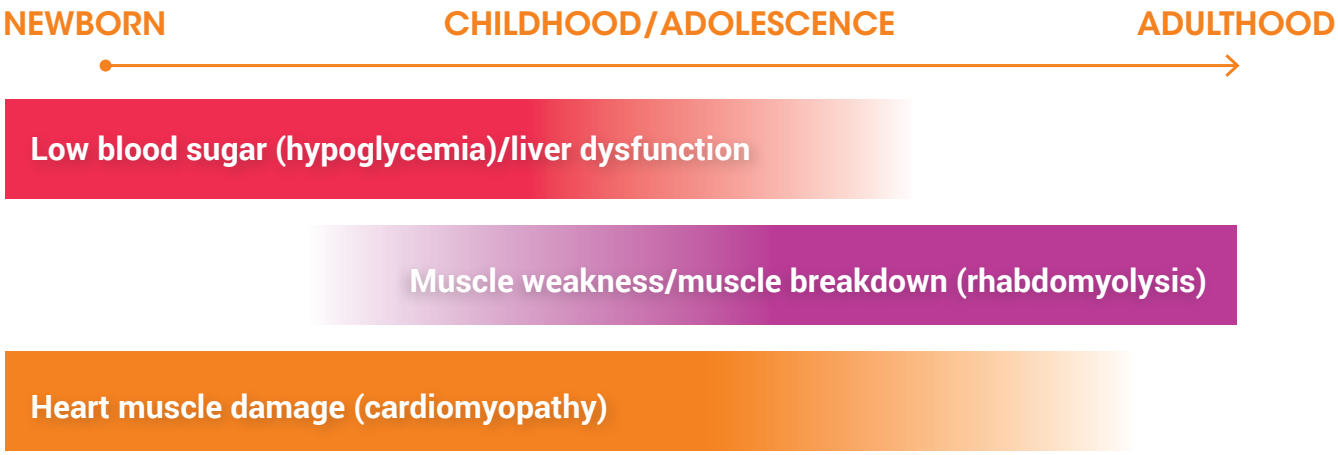
THE IMPACT

Patients with LC-FAOD face difficult challenges and substantial medical burdens[4,9,15-17]

- When energy balance is disrupted, **acute episodes** and **chronic symptoms** burden patients[4,9,15-17]
- Acute episodes may occur **spontaneously** and **unpredictably** in some LC-FAOD types, with long-lasting implications[3,4,15]

DESPITE EARLY DETECTION AND MANAGEMENT, LC-FAOD MORTALITY RATES TEND TO REMAIN HIGH.[9]

A SPECTRUM OF PRESENTATION



- Although symptoms can appear **within a few hours of birth**, they may also **not appear until adulthood**[4,18,19]
- Symptoms can **evolve over time** and may differ depending on when they appear[4,18,19]
- Symptoms are **episodic** in nature and can lead to hospitalizations, emergency room visits, and emergency interventions, and can be **life threatening**[9,15,20]
- **Heterogeneity** of signs and symptoms is common, within each LC-FAOD type or even between affected individuals in the same family[21]

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